REMARKS/ARGUMENTS

Reconsideration and allowance of the pending claims is respectfully requested in light of the remarks which follow. Claims 1 and 9 have been amended. Support for the amendment of claim 1 may be found, for instance, in the specification at page 36, lines 14; and page 49, line 33. Support for the amendment of claim 9 may be found, for instance, at page 7, line 5. Upon entry of this amendment, claims 1, 7, 9, 11-14, 18-22, and 25-30 will be pending.

Claim rejections under 35 U.S.C. § 103(a)

Claims 1, 4, 8-9, 11-14, 18-22, and 25-30 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Leppla *et al.* (U.S. Patent No. 5,677,274) ("Leppla") as evidenced by Klimpel *et al.* (PNAS, 89:10277-10281 (1992)) ("Klimpel") in view of Bayley *et al.* (U.S. Patent No. 5,817,771) ("Bayley"). To the extent that this rejection applies to the amended claims, Applicants respectfully traverse.

The Supreme Court has affirmed the analysis set forth in *Graham* for the determination of obviousness. *See KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007). Specifically, the Supreme Court, quoting from *Graham*, stated:

> Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject is determined. Such secondary considerations as commercial success, long felt but unresolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented. *Id.* at 1734.

Furthermore, the Court preserved the teaching, suggestion, and motivation (TSM) test, stating "[t]here is no necessary inconsistency between the idea underlying the TSM test and the *Graham* analysis", noting that it is "important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed invention does." *Id.* at 1741; *see also*, USPTO memorandum on *KSR v. Teleflex*, dated May 3, 2007.

Thus, there continues to be a requirement that a motivation to combine the teachings must be explicitly and clearly stated by the Patent Office in making an obviousness rejection. The USPTO memorandum is in agreement, stating "[t]herefore in formulating a rejection under 35 U.S.C. § 103(a) based upon a combination of prior art elements, it remains necessary to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed". *See* USPTO memorandum on *KSR v. Teleflex*, dated May 3, 2007.

Moreover, as set forth in M.P.E.P. § 2143, "[t]o establish a *prima facie* case of obviousness, *three* basic criteria must be met: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference (or references when combined) must teach or suggest all the claim limitations." All three elements set forth above must be present in order to establish a *prima facie* case of obviousness.

Among the secondary considerations specifically discussed in *KSR*, the Court emphasized surprising or unexpected results as being indicative of non-obviousness. *Id.* at 1740, citing to *U.S. v. Adams*, 383 U.S. 39, 40 (1996) ("The fact that the elements worked together in an unexpected and fruitful manner supported the conclusion that Adam's design was not obvious to those skilled in the art".) Furthermore, as stated in M.P.E.P. § 716.01(a), "[a]ffidavits or declarations, when timely presented, containing evidence of criticality or unexpected results, commercial success, long-felt but unsolved needs, failure of others, skepticism of experts, etc., must be considered by the examiner in determining the issue of obviousness of claims for patentability under 35 U.S.C. 103." Moreover, "a greater than expected result is an evidentiary factor pertinent to the legal conclusion of obviousness . . . of the claims at issue." M.P.E.P. § 716.02(a).

In *KSR*, the Court also cautioned against the use of impermissible hindsight. *KSR* at 1742. ("A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning.")

Thus, the *Graham* factors, including the use of objective evidence of secondary considerations to rebut a *prima facie* case of obviousness, as well as, a flexible use of the TSM test remains the framework to be followed for a determination of obviousness.

1. The claimed invention

The claimed invention is directed to methods of targeting a compound to a cell using a mutant protective antigen. More particularly, the invention is directed to targeting a compound to a carcinoma or fibrosarcoma cell over-expressing a plasminogen activator (uPA) and plasminogen activator receptor (uPAR) by administering to the carcinoma or fibrocarcinoma cell (1) a mutant protective antigen protein comprising a uPA-recognized cleavage site in place of the native protective antigen furin-recognized cleavage site, wherein the mutant protective antigen is cleaved by uPA; and (2) a compound comprising a lethal factor polypeptide comprising a protective antigen binding site; wherein the lethal factor polypeptide binds to cleaved protective antigen and is translocated into the carcinoma or fibrosarcoma cell, thereby delivering the compound to these cells.

2. The combined references do not teach each and every element of the claimed invention

Applicants respectfully submit that the combination of cited references does not teach each and every element of the claimed invention as currently amended.

Bayley sets forth a prophetic example disclosing potential antibody-αHL conjugates that would be activated by proteases to generate pore-forming agents. Figure 10 of Bayley shows a schematic hypothetical example of an inactive αHL conjugate, comprising an antibody and a site for tumor-specific protease cleavage to generate an active pore-forming agent upon proteolytic cleavage. While Bayley states that proteases such as urokinase-type plasminogen activator (uPA) are associated with the metastatic phenotype of cancer cells, Bayley only discloses a single type of cancer cell - melanoma.

Leppla discloses a method of "killing a tumor cell in a subject", without any disclosure of any particular types of tumor cells. Kimpel discloses the cell surface cleavage of PA by rat myoblast L6 cells and cytotoxicity of mutated PA proteins in the presence of LF using

macrophage cells (RAW264.7 or J774A.1); thus, Kimpel does not disclose any cancer cells whatsoever.

Applicants have amended claim 1 to recite, in part, the targeting of carcinoma or fibrosarcoma cells. None of the cited references, singly or in combination, teach or suggest this element of claim 1 as amended. Thus, at a minimum, the cited references do not teach or suggest all the claim limitations of amended claim 1, as required to establish a *prima facie* case of obviousness. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

3. The skilled artisan would have no reasonable expectation of success in combining the cited references.

The Examiner alleges that "[o]ne of ordinary skill in the art would have a reasonable expectation of success that by combining the plasminogen activator-recognized cleavage site of Bayley *et al.* with the method of specifically targeting a bioactive compound as taught by Leppla *et al.*, one would achieve a method of specifically targeting a compound to a cancer cell because as evidenced by Bayley *et al.*, cancer cells have been shown to secrete plasminogen activator". The Examiner further states that "[Bayley] teaches that uPA is highly expressed in melanoma cells". *See* Office Action at page 4. For the reasons discussed below, Applicants submit that the skilled artisan would have no reasonable expectation of success in combining the cited references to arrive at the currently claimed invention.

It has long been acknowledged that the fields of chemistry and biotechnology represent unpredictable arts. *See, e.g.*, MPEP 2164.03. Because of this unpredictability, the skilled artisan would not have had a reasonable expectation that substituting the native furin cleavage site in protective antigen, as taught by Leppla, with a tumor protease cleavage site, such as the uPA cleavage site, as taught by Bayley would result in a composition that would target a compound to carcinoma or fibrosarcoma, as presently claimed.

As discussed in detail above, Bayley discloses hypothetically that antibody-αHL conjugates containing a tumor specific protease cleavage sequence might be used to generate an active pore forming agent upon cleavage by a tumor specific protease. Bayley suggests that uPA

might be such a tumor specific protease, citing its expression in metastatic tumor cells, with reference to a single cancer cell type - melanoma.

The cited portion of Leppla teaches the killing of a tumor cell by administration of "a first fusion protein comprising the translocation domain and LF binding domain of the native PA protein and a tumor cell specific ligand domain" and "a second fusion protein . . . compris[ing] the PA binding domain of the native LF protein and a cytotoxic domain of a non-LF protein". (Emphasis added.) *See* Leppla at column 15, lines 27-37. Thus, with respect to the treatment of tumor cells, Leppla is silent with regard to switching the native furin site with a tumor specific protease site. The principal disclosure in Leppla is directed to the treatment of HIV infected cells, using a PA protein in which the furin cleavage site has been replaced with the HIV-1 protease site.

As explained below, the disclosures of the cited references would not provide the skilled artisan with a reasonable expectation of success in combining the cited references to arrive at the presently claimed invention.

The skilled artisan would recognize that in order to solve the problem of targeting a compound to a cancer cell over-expressing uPA and uPAR, using a mutant protective antigen protein comprising a uPA-recognized cleavage site in place of the native protective antigen furin-recognized cleavage site, as presently claimed, a number of conditions must be met. First, the cell must express uPA and uPAR (the cell surface receptor for uPA). Secondly, the secreted uPA, upon binding to the cell surface uPA receptor to form a uPA/uPAR complex, must be in sufficient proximity and in the right three dimensional configuration to the mutant protective antigen protein containing a uPA-recognized cleavage site in order to effect cleavage. Thirdly, the non-natively disposed uPA-recognized cleavage site on the mutant protective antigen must be in the proper three dimensional configuration to allow recognition and cleavage by the uPA/uPAR complex.

As Dr. Leppla explains, the three dimensional structures of both a protease and its substrate are critical for the binding of a protease to its substrate and subsequent proteolytic cleavage (*see* Declaration ¶ 7). Given the highly structured nature of plasminogen, the skilled artisan would not have expected the uPA cleavage site to adopt its native three dimensional

structure when taken out of its normal context within plasminogen and placed into a heterologous, non-native context such as in protective antigen. Dr. Leppla explains that in view of the constrained nature of uPA upon binding to cell surface uPAR, one of skill in the art would not have expected the non-natively situated uPA cleavage site on the mutant protective antigen to come into contact with the uPA/uPAR complex (*see* Declaration ¶ 7), citing as one rationale the fact that the uPA cleavage site in the mutant protective antigen might not be positioned at an appropriate distance from the cell membrane to contact the uPA on the surface of the target cell (*see* Declaration ¶ 7). Accordingly, Dr Leppla concludes that there would be no cleavage of the mutant protective antigen by uPA or delivery of a compound to the target cell (*see* Declaration ¶ 7). Thus, the skilled artisan would believe that these references would not fulfill at least two of the conditions that must be met – correct three dimensional structure of the cleavage site and proximity to the protease - in order for the combination proposed by the invention to be operable.

Thus, the skilled artisan would have numerous doubts that a simple swap of the native furin site in protective antigen with the uPA-recognized cleavage site would necessarily result in a mutant protective antigen that is cleavable by the uPA/uPAR complex. The skilled artisan would recognize that the native substrate for uPA, plasminogen, is a highly structured and large 90 kDa protein, containing numerous structure determining disulfide bonds. Although the exact three dimensional structure of plasminogen was not known at the time of filing, it was known that this protein contained numerous structural elements, termed kringle domains, which have numerous interdomain disulfide bonds. Given the highly structured nature of uPA's normal plasminogen substrate, the skilled artisan would doubt that the proper structure of the uPA cleavage site would be maintained upon engrafting it onto an unrelated protein.

In the making this rejection, the Examiner appears to be using impermissible hindsight reconstruction in combining these references. As stated by the MPEP, "the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination." *See* MPEP 2143.01(III). As discussed in Dr. Leppla's declaration, the references would fail to suggest to the skilled artisan the desirability of placing the uPA cleavage site in the context of protective antigen.

Rather, by combining these references, the skilled practitioner would, in fact, be "proceeding contrary to accepted wisdom in the art". *See* MPEP 2145.

Finally, the cited references, in particular, Bayley, mention only one type of cancer cell, melanoma, that even expresses uPA. Thus, the cited references provide only one example, a prophetic one at that, of a cancer cell for which the combined teachings of the references might work. Given the unpredictability of the biotechnological arts and the heterogeneous nature of cancer cells derived from different tissues and as a result of different genetic abnormalities, it would not be obvious to the skilled artisan what types of cancer cells would be sensitive to the mutant PA and LF constructs of the present invention. Applicants submit that the disclosure of the present invention provides the first demonstration that a mutant protective antigen containing a uPA cleavable site can be used to deliver a compound to a carcinoma or fibrosarcoma cell overexpressing a urokinase-type plasminogen activator.

4. Dr. Leppla's declaration provides objective secondary evidence of non-obviousness

As discussed above, objective secondary evidence of non-obviousness can be provided by the demonstration of unexpected results. As discussed by the Court in *KSR*, such evidence of unexpected or surprising results provides a strong indication of non-obviousness. Applicants respectfully submit that the data presented in Dr. Leppla's previously submitted declaration unequivocally demonstrates that the claimed mutant protective antigens are surprisingly effective for the delivery of a compound to tumors overexpressing uPA *in vivo* (*see* Declaration ¶ 8), for instance, to the cancer cells, carcinoma and fibrosarcoma, as currently recited in the amended claims. As discussed in Dr. Leppla's declaration, when the mutant protective antigens comprising a uPA cleavage site were systemically administered to mice bearing one of the tumor types, B16 melanoma, T241 fibrosarcoma, or Lewis lung carcinoma, all of which overexpress uPA, highly significant tumor inhibition was observed (*see* Declaration ¶ 8). (Emphasis added.) Claim 1 has been amended to specifically recite carcinoma and fibrosarcoma, two of the cancer types for which highly significant tumor inhibition was observed.

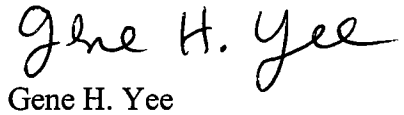
In light of the foregoing, Applicants urge the Examiner to reconsider the evidence of unexpected results presented in Dr. Leppla's declaration as evidence of nonobviousness, in light of claim 1 as amended, and then withdraw the rejection under 35 U.S.C. § 103(a).

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



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